Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Taggart DP, Altman DG, Gray AM, et al. Randomized trial of bilateral versus single internal-thoracic-artery grafts. N Engl J Med. DOI: 10.1056/NEJMoa1610021

SUPPLEMENTARY APPENDIX

Centres participating in Arterial Revascularisation Trial (ART). Principal Investigators in bold, co-investigators (number of patients enrolled).

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3. Edinburgh Royal Infirmary, Edinburgh, UK. **V Zamvar,** D Ezakadan (217)
4. Austin and Repatriation Medical Centre, Melbourne, Australia**. B Buxton**, **S Seevanayagam**, G Matalanis, A Rosalion, J Negri, S Moten, V Atkinson, A Newcomb, P Polidano, R Pana, S Gerbo (192)
5. University Hospital of Wales, Cardiff, UK, **P O'Keefe**, U von Oppell, D Mehta, A Azzu, A Szafranek, E Kulatilake, J Evans, N Martin, D Banner (185)
6. Royal Sussex County, Brighton, UK. **U Trivedi, A Forsyth**, J Hyde, A Cohen, M Lewis, E Gardner, A MacKenzie, N Cooter, E Joyce, J Parker, F Champney (180)
7. Freeman Hospital, Newcastle, UK. **S Clark**, J Dark, K Tocewicz, T Pillay, S Rowling, J Adams-Hall (152)
8. Medical University of Silesia (1st Department of Cardiac Surgery), Katowice, Poland. **A Bochenek,** M Cisowski, M Bolkowski, W Morawski, M Guc, M Krejca , M Wilczynski, A Duralek, W Gerber, J Skarysz, R Shrestha, W Swiech, P Szmagala, L Krzych, A Pawlak, K Kepa (145)
9. Royal Infirmary, Manchester, UK. **R Hasan**, D Keenan, B Prendergast, N Odom, K McLaughlin, G Cummings-Fosong, C Mathew, H Iles-Smith, A Oomen (115)
10. King's College Hospital, London, UK. **J Desai,** A El-Gamel, L John, O Wendler, M Andrews, K Rance, R Williams, V Hogervorst, J Gregory, J Jessup, A Knighton, A Hoare (114)
11. Papworth Hospital, Cambridge, UK. **A Ritchie, C Choong, S Nair,** D Jenkins, S Large, **C Sudarshan**, M Barman, K Dhital, T Routledge, B Rosengard, H Munday, K Rintoul, E Jarrett, S Lao-Sirieix, A Wilkinson, L Garner, J Osmond, H Holcombe (101)
12. Castle Hill Hospital, Hull, UK. **A Cale**, S Griffin, J Dickson, J Cook (97)
13. Glenfield Hospital, Leicester, UK. **T Spyt,** M Hickey, A Sosnowski, G Peek, J Szostek, L Hadjinikalaou, E Logtens, M Oakley, S Leji (95)
14. Harefield Hospital, London, UK. **J Gaer,** M Amrani, G Dreyfus, T Bahrami, F de Robertis, K Baig, G Asimakopoulos,H Vohra, V Pai, S Tadjkarimi, Soleimani, G Stavri, G Bull, H Collappen (94)
15. John Paul II, Krakow, Poland. **J Sadowksi**, B Gaweda, P Rudzinski, J Stolinski, J Konstanty-Kalandyk (92)
16. Heart Institute of Pernambuco, Recife, Brazil. **F Moraes,** C Moraes, J Wanderley (82)
17. Royal Brompton Hospital, London, UK. **J Pepper**, A De Souza, M Petrou, R Trimlett, T Morgan, J Gavino, SF Wang (82)
18. St George's Hospital, London, UK. **V Chandrasekaran**, R Kanagasaby, M Sarsam, H Ryan, L Billings, L Ruddick, A Achampong, E Forster (78)

19. Medical University of Gdansk, Gdansk, Poland. **R Pawlaczyk**, P Siondalski, J Rogowski, K Roszak, K Jarmoszewicz, D Jagielak, S Gafka (74)
20. Care Hospital, Hyderabad, India. **G Mannam,** Naguboyin, L Rao Sajja, B Dandu (69)
21. Northern General Hospital, Sheffield, UK. **N Briffa**, P Braidley, G Cooper, A Knighton, K Allen, G Sangha, C Bridge, H McMellon (67)
22. Ospedale Mauriziano, Turin, Italy. **R Casabona**, **G Actis Dato**, G Bardi, S Del Ponte, Forsennati, F Parisi, G Punta, R Flocco, F Sansone, E Zingarelli (60)
23. The Cardiothoracic Centre, Liverpool, UK. **W Dihmis, M Kuduvali,** C Prince, H Rogers, L McQuade (50)
24. Szpital Uniwersytecki, Bydgoszcz, Poland. **L Anisimowicz**, M Bokszanski, W Pawliszak, J Kolakowski, G Lau, W Ogorzeja, I Gumanska, P Kulinski (23)
25. Landesklinikum, St Polten, Austria. **B Podesser,** K Trescher, O Bernecker, Ch Holzinger, K Binder, I Schor, P Bergmann, H Kassal, B Motovova (20)
26. Escorts Heart Institute, New Delhi, India. **N Trehan, Z Meharwal,** R Malhotra, M Goel, B Kumer, S Bazaz, N Bake, A Singh, Y Mishka, R Gupta, S Basumatary (19)
27. Silesian Centre for Heart Disease, Zabrze, Poland. **M Zembala**, B Szafron, J Pacholewicz, M Krason, Farmas, Wojarski, Zych (10)
28. Szpital Wojewodzki 2, Rzeszow, Poland**. K Widenka,** I Szymanik, M Kolwca, W Mazur, A Kurowicki, S Zurek, T Stacel, I Jaworska (6)

Trial Steering Committee

1. Professor P Sleight, Emeritus Professor Cardiovascular Medicine, Oxford, UK (Chairman)
2. Professor D Altman, Professor of Statistics in Medicine, Oxford, UK
3. Professor K Channon, Professor of Cardiovascular Medicine, Oxford, UK
4. Professor J Dark, Professor of Cardiac Surgery, Newcastle, UK
5. Ms B Farrell, Trials Director, National Perinatal Epidemiology Unit, Oxford, UK
6. Dr M Flather, Professor of Medicine and Clinical Trials, Norwich, UK
7. Professor A Gray, Professor of Health Economics, Oxford, UK
8. Professor J Pepper, Professor of Cardiac Surgery, London, UK
9. Dr R Stables, Consultant Cardiologist, Liverpool, UK
10. Professor D Taggart Consultant Cardiac Surgeon, Oxford, UK (Chief Investigator)
11. The late Professor G Vermes, Emeritus Professor of Hebrew Studies, Oxford, UK (Patient Lay Member)
12. Professor J Pearson British Heart Foundation, London, UK (Observer)
13. Dr M Pitman, Medical Research Council, London, UK (Observer)
14. Dr Belinda Lees, Trials Coordinator, Oxford UK (Observer)

Data Monitoring Committee

1. Professor S Yusuf, Professor of Medicine, Hamilton, Canada (Chairman)
2. Professor S Pocock, Professor of Medical Statistics, London, UK
3. Professor D Julian, Emeritus Professor of Cardiology, London, UK
4. Professor T Treasure, Professor of Cardiothoracic Surgery, London, UK

Clinical Event Adjudicators

1. Mr U Trivedi, Royal Sussex County Hospital, Brighton, UK
2. Mr P O'Keefe, University Hospital of Wales, Cardiff, UK
3. Professor U Von Oppel, University Hospital of Wales, Cardiff, UK
4. Mr V Zamvar, Edinburgh Royal Infirmary, Edinburgh, UK
5. Mr A Cale, Castle Hill Hospital, Hull, UK
6. Mr M Hickey, Glenfield Hospital, Leicester, UK
7. Mr T Spyt, Glenfield Hospital, Leicester, UK
8. Professor J Pepper, Royal Brompton Hospital, London, UK
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10. Mr T Pillay, Freeman Hospital, Newcastle, UK
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13. Prof M Flather, University of East Anglia, Norwich, UK
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18. Dr D Kotecha, University of Birmingham, Birmingham UK
19. Dr K Qureshi, London Chest Hospital, London, UK
20. Dr L Krzych, Medical University Of Silesia, Katowice, Poland
21. Dr T Geisler, University Hospital Tuebingen, Tuebingen, Germany
22. Mr N Briffa, Northern General Hospital, Sheffield, UK
23. Dr L Manzano-Espinosa, Hospital Universitario Ramón y Cajal Madrid, Spain
24. Dr M Jasinski, Medical University Of Silesia, Katowice, Poland

Definitions of Serious Adverse Events used in ART

1. Death

(a) Death due to cardiac causes:
Cardiac causes of death such as congestive heart failure, arrhythmia or myocardial infarction.
(b) Other vascular causes of death:
Vascular causes of death such as pulmonary embolus, dissection, cerebrovascular accident or bleeding event.
(c) Non-cardiovascular causes of death:
This includes any other cause of death

2. Major Bleed

A major bleeding event is defined as requiring the use of blood products or a surgical procedure to deal with the bleed or its sequelae.

3. Cerebrovascular Accident (CVA)

A CVA is defined as a new focal neurological deficit thought to be vascular in origin with signs and symptoms lasting more than 24 hours.

4. Revascularization

For the purpose of the trial a revascularization is described as a Coronary Artery Bypass Graft (CABG) or Percutaneous Coronary Intervention (PCI) after the trial procedure.

5. Myocardial Infarction (MI)

(a) Non peri-procedural MI
MI definition (2 out of the following 3 criteria must be present)

- New onset or worsening pattern of characteristic ischemic chest pain occurring at rest or with minimal exercise lasting longer than 20 minutes and requiring nitrates or narcotic analgesia for relief of pain.
- Elevation of cardiac markers (CK, CK-MB or Troponin) to at least twice the upper limit of the normal reference range (or greater than 20% of the previous value if already elevated in the context of early hospital MI).
- ECG changes compatible with ischemia

(b) MI within 48 hours of PTCA
MI post-PTCA defined as:

- the standard as above (at least 2 of 3 criteria)

or

- elevation of cardiac markers to at least 3 x the upper limit of normal

(c) MI within 72 hours of CABG
MI post-CABG defined as:

- elevation of cardiac markers to at least 5 x the upper limit of normal

or

- development of new pathological Q waves in at least two contiguous leads.

Other Serious Adverse Events

A "Serious Adverse Event" is defined as requiring or prolonging hospital admission for medical reasons. The hospitalization does not have to be related to the study procedure or patient's underlying cardiovascular disease for it to constitute an "Other SAE".

Supplementary Appendix Table S1
Details of surgical procedure, post-operative care and hospital stay

Procedures	**Single graft group**	**Bilateral graft group**
Details of operation	(n=1546)	(n=1531)
On pump	928 (60.0%)	890 (58.1%)
Off pump	618 (40.0%)	641 (41.9%)
Intra-operative conversions to bypass	13/618 (2.1%)	15/641 (2.3%)
Mean (SD) duration of operation, mins	199 (58)	222 (61)
Median (IQR)	190 (160 to 250)	215 (185 to 250)
Number of vessels grafted	(n=1546)	(n=1530)
1	11 (0.7%)	8 (0.5%)
2	273 (17.7%)	272 (17.8%)
3	749 (48.54%)	771 (50.4%)
4+	513 (33.2%)	479 (31.3%)
Blood products used during surgery		
Aprotinin started during surgery	372/1545 (24.1%)	368/1531 (24.0%)
Aprotinin given after surgery	89/1545 (5.8%)	98/1530 (6.4%)
Blood transfusion	184/1515 (12.2%)	179/1492 (12.0%)
Median (IQR) blood (red cells)	500 (300 to 600))	500 (300 to600)
Platelets	35/1512 (2.3%)	46/1494 (3.1%)
Fresh Frozen Plasma (FFP)	53/1513 (3.5%)	66/1493 (4.4%)
Cell saver	474/1500 (31.6%)	461/1479 (31.2%)
Immediate post-operative period		
Return to theatre and reason	54/1546 (3.5%)	66/1532 (4.3%)
Bleeding	*44*	*51*
Tamponade	*2*	*6*
Other	*8*	*9*
Unknown	*3*	*6*
Intra-aortic balloon pump used (IABP)	57/1546 (3.7%)	68/1532 (4.4%)
Renal support therapy	68/1545 (4.4%)	91/1532 (5.9%)
	(n=1539)	(n=1524)
Mean (SD) Duration of ventilation (minutes)	863 (3293)	968 (3029)
Median (IQR)	580 (335-830)	598 (360 to 890)
Pre-discharge details	(n=1447)	(n=1429)

ITU admissions: 0	8 (0.6%)	8 (0.6%)
1	1390 (96.1%)	1362 (95.3%)
2 or more	49 (3.4%)	59 (4.1%)
	(n=1551)	(n=1538)
Mean (SD) ITU length of stay (hours)	38 (106)	41 (94)
Median (IQR)	22 (16 to 43)	22 (15 to 45)
Mean (SD) HDU length of stay (days)	2 (3.7)	2 (3.8)
Median (IQR)	1 (1 to 2)	1 (1 to 2)
Mean (SD) post-operative total hospital stay (days)	7.5 (7.6)	8.0 (7.4)
Median (IQR)	6 (5 to 8)	6.5 (5 to 8)

ITU = intensive therapy unit; HDU = high dependency unit, IQR = interquartile range

Supplementary Appendix Table S2

Medications at 5 years

Medication [n (%)]	Single graft group (n=1176)	Bilateral graft group (n=1179)
Aspirin	89.2%	88.6%
Clopidogrel	10.7%	9.1%
Warfarin	5.5%	5.2%
Other anticoagulant	0.9%	1.2%
Beta-blockers	78.3%	74.1%
Calcium-channel antagonist	17.3%	18.7%
Nitrates	7.5%	8.4%
Potassium channel activators	2.9%	3.2%
Statins	90.1%	88.0%
Other lipid lowering agent	5.1%	5.8%
ACE inhibitor	57.4%	58.1%
Angiotensin-II receptor blocker	15.3%	15.9%
Diuretics	20.2%	19.1%
Digoxin	2.2%	1.0%
Amiodarone	1.0%	1.3%

*Medication information is provided for those with complete case report form data at 5 years. There are no significant differences in treatment frequencies between the two groups except Digoxin $p<0.05$

Supplementary Appendix Table S3

Classification of causes of death

Cause of death	Single graft group (n=1554)	Bilateral graft group (n=1548)	Subdistribution Hazard Ratio (95% CI)	P value
Cardiac	42 (2.7%)	42 (2.7%)	1.00 (0.65, 1.54)	0.98
Non CV	64 (4.1%)	67 (4.3%)	1.05 (0.75, 1.49)	0.76
Other vascular	13 (0.8%)	13 (0.8%)	1.01 (0.47, 2.17)	0.99
Unable to classify	11 (0.7%)	12 (0.8%)	1.10 (0.49, 2.49)	0.82

Hazard ratios use the single graft group as the control

Supplementary Appendix Table S4
Per protocol (comparison based on patients who actually received assigned treatment) and "as-treated" (based on the actual operation carried out) analyses

Outcome	Single graft group N	Bilateral graft group N	Deaths Single graft group	Deaths Bilateral graft group	Hazard Ratio (95% CI)	P value
Primary – ITT unadjusted	1554	1548	130 (8.4%)	134 (8.7%)	1.04 (0.81, 1.32)	0.77
ITT – adjusted	1554	1548	130 (8.4%)	134 (8.7%)	1.03 (0.81, 1.32)	0.80
Per protocol – unadjusted	1494	1294	125 (8.4%)	105 (8.1%)	0.97 (0.75, 1.25)	0.81
Per protocol – adjusted*	1494	1294	125 (8.4%)	105 (8.1%)	1.01 (0.78, 1.31)	0.95
As-treated – unadjusted	1709	1332	149 (8.7%)	107 (8.0%)	0.92 (0.72, 1.18)	0.50
As-treated – adjusted*	1709	1332	149 (8.7%)	107 (8.0%)	0.98 (0.76, 1.26)	0.87

***** Adjusted for age, gender, diabetes and ejection fraction
Hazard ratios use the single graft group as the control

Supplementary Table S5. Health related quality of life assessed at 5 years

Measure	Single graft group N=1124§	Bilateral graft group N=1128§	P value
Shortened WHO Rose Angina Questionnaire:			
Do you ever have any pain or discomfort in your chest?			
Yes (%)	317 (28.9%)	353 (32.1%)	0.11
No (%)	780 (71.1%)	748 (67.9%)	
Missing	27	17	
When you walk at an ordinary pace on the level does this produce the pain?*			
Yes (%)	74 (23.9%)	83 (24.3%)	0.51
No (%)	230 (74.2%)	256 (74.9%)	
Unable (%)	6 (1.9%)	3 (0.8%)	
Missing	7	11	
When you walk uphill or hurry does this produce the pain?*			
Yes (%)	192 (62.3%)	221 (65.0%)	0.67
No (%)	104 (33.8%)	104 (30.6%)	
Unable (%)	12 (3.9%)	15 (4.4%)	
Missing	9	13	
EQ-5D			
Mean (SD) index score (1=full health, 0=dead)	0.811 (0.251)	0.819 (0.237)	0.47
SF-36 **, Mean (SD)			
Physical functioning	72 (28)	71 (28)	
Role-physical	72 (30)	72 (30)	
Bodily Pain	81 (22)	81 (22.5)	
General Health	63 (23)	62 (23)	
Vitality	60 (22)	58 (23)	
Social Functioning	81 (27)	81 (26)	
Role - Emotional	82 (27)	81 (26)	
Mental Health	77 (18)	77 (18)	

§ All analyses based on numbers of patients providing data; no imputation was performed for missing data. Numbers available for analysis vary slightly for SF-36 domains * Responses reported only for patients answering Yes to question 1 on the Shortened WHO Rose Angina Questionnaire (WHO = World Health Organisation) ** No significant differences in SF-36 scores